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(71) Applicant *(for all designated States except US)*: THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : KOH, Keiko [JP/JP]; 17-5, Azuma 3-chome, Tsukuba-shi, Ibaragi-ken 305 (JP). TSUZUKI, Kazuo [JP/JP]; 1054-19, Yatabe, Tsukuba-shi, Ibaragi-ken 305 (JP). TANIGUCHI, Mikio [JP/JP]; 668-34, Shimohirooka, Tsukuba-shi, Ibaragi-ken 305 (JP). KUSHIDA, Hiroshi [JP/JP]; 1305-157, Oaza-Tomado, Shimodate-shi, Ibaragi-ken 308 (JP). OZAWA, Kazunori [JP/JP]; 17-5, Azuma 3-chome, Tsukuba-shi, Ibaragi-ken 305 (JP).

(74) Agent: WELCH, Lawrence, T.; Corporate Patents & Trademarks, The Upjohn Company, Kalamazoo, MI 49001 (US).

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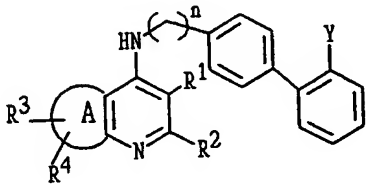
(54) Title: 4-AMINOQUINOLINES AND PHARMACEUTICAL COMPOSITIONS THEREOF



(1)

(57) Abstract

The present invention provides a compound represented by general formula (1), or a pharmacologically acceptable ester or salt thereof, as well as a composition for preventing or treating hypertension or congestive heart failure which comprises the compound as an active ingredient. These compounds are well absorbed and have long-lasting action.

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4-AMINOQUINOLINES AND PHARMACEUTICAL COMPOSITIONS THEREOF

FIELD OF THE INVENTION

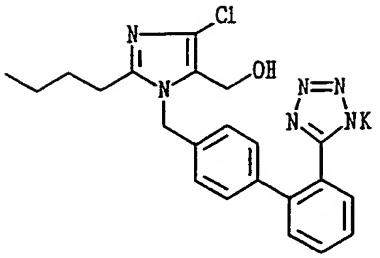
The present invention relates to novel 4-aminoquinoline or a pharmacologically acceptable ester or salt thereof and a pharmeceutical composition for preventing or treating hypertension or congestive heart failure which comprises the same as an active ingredient.

BACKGROUND OF THE INVENTION

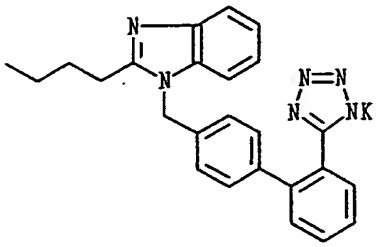
It is widely known that Renin-Angiotensin-Aldosterone system is closely connected with hypertensive pathogeny or pathemia through control of blood pressure and amount of fluid or electrolyte. Prevention and treatment of hypertension including essential hypertension and further congestive heart failure by controlling this system have been studied for a long time. As the controlling methods, there are i) inhibition of synthesis or secretion of renin which is thought to be the first part of the system, ii) inhibition of the reaction between renin and a substrate of renin (angiotensinogen) to decrease angiotensin I which is the reaction product, iii) inhibition of an enzyme which converts angiotensin I into angiotensin II having strong vasoconstriction action, aldosterone secretion stimulating action, sympathetic nerve function promoting action and the like (angiotensin converting enzyme: ACE), iv) inhibition of the action of the produced angiotensin II by blocking a receptor part thereof, v) activation of angiotensinase which rapidly degrades the produced angiotensin II and the like.

Among them, the study of ACE inhibitors is most advanced, and many such drugs are used for preventing or treating hypertension or congestive heart failure. However, since the ACE inhibitors are not selective and act toward other systems such as kalliklein-kinin system and the like, there is a clinical problem in that side effects such as skin rash and dry cough occur frequently. For this reason, there have been many attempts to develop a renin inhibitor, which is thought to be more selective, have been tried, but have not been successfully marketed.

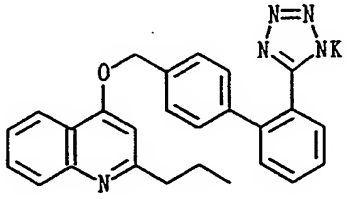
The putative peptidic Angiotensin II antagonist Saralasin has been available for over 30 years. However, its therapeutic use has been severely limited by its partial agonistic action, short plasma half-life and lack of oral activity. Since the discovery of a "non-peptide" Angiotensin II antagonist by Takeda (Japan Kokai Patent 1979-148,788, 1981-71,073, 1982-98,270, 1983-157,768), extensive efforts have been made to modify or optimize this prototype lead especially by Dupont. These are reported in EP-A0253310 and EP-A0291969, and the compound known as Dup753 is currently being clinically tested. The structure of Dup753 is set out below:



However, since this compound is usually produced as 1:1 positional isomer upon N-alkylation, Dup753 can not be selectively synthetized unless a special process is used, and this is thought to be a problem for mass production. On the other hand, it was thought to be effective at that time that the 5-position of the imidazole should have a polar group for increasing the phramacological activity. This thinking was compelled to be significantly modified by the finding of benzimidazoles shown in EP-A-0392317 (also reported in EP-A-0400835 and EP-A-0399732 later). Further, this was developed into imidazopyridines (see EP-A-0399731, EP-A-0400974 and EP-A-01415886).



Recently, 4-oxyquinoline derivatives having no these imidazole rings are reported to have angiotensin II antagonist activity (EP-A-0412848).



On the other hand, 4-aminoquinoline derivatives are reported to be effective for treating gastrointestinal failure such as gastric ulcer (EP-A-387821) or for improving anamensis (US-4942168), but not to have angiotensin II antagonist activity.

PROBLEMS TO BE SOLVED BY THE INVENTION

From the above described point of view, and paying attention to Angiotensin II antagonist as an agent for preventing or treating hypertension or congestive heart failure, the present inventors had been studied hard on drugs which has higher activity, good absorbability into the body upon oral administration and long-lasting aciton, and as a result, we have found out that certain 4-aminoquinolines are effective, which resulted in completion of the present

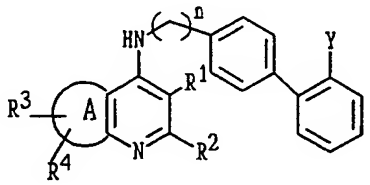
invention.

INFORMATION DISCLOSURE

A number of imidazo containing moieties are disclosed as useful in the treatment of hypertension as described above, see, e.g., Japanese Kokai patent application 78/148,788; 81/71,073; 82/98,270 and 83/157,768; published European patent applications EPA 253310; 291969; 392317; 400835; 399732; 399731; 400974; and 415886. Certain 4-aminoquinolines are disclosed in EPA 387821 and U.S. Patent No. 4,942,168. EPA 412848 discloses certain 4-oxyquindine derivatives having angiotensin II antagonist activity.

MEANS OF SOLVING THE PROBLEMS

The present invention provides a 4-aminoquinoline represented by the general formula [1]:



wherein A is benzene, pyridine, pyridazine, pyrimidine or pyrazine ring, wherein each ring is fused to the pyridine ring;

R^1 and R^2 are independently a C_1-C_8 alkyl group, a C_2-C_8 alkenyl group, a C_2-C_8 alkynyl group or -CF_3 group;

Y is a 1H-tetrazol-5-yl group or an alkali metal salt thereof, a -CO_2R^5 group, a -CONR'R" or a -$CONHSO_2R^6$ group;

R^3 and R^4 are independently a hydrogen atom, an opitonally substituted C_1-C_8 alkyl group, a C_1-C_8 alkoxy, hydroxy, a halogen atom, -CN group, a -SO_2NR'R" group, a -CO_2R^5 group, a -CONR'R" group, -$CONHSO_2R^6$ group or a 1H-tetrazol-5-yl group or an alkali metal salt thereof;

wherein R^5 is a hydrogen atom, an alkali metal atom, a C_1-C_8 alkyl group;

R^6 is a C_1-C_8 alkyl group, a C_3-C_{10} cycloalkyl group or an aryl group;

wherein R' and R" are independently a hydrogen atom or a C_1-C_8 alkyl group, or R' and R" together form an alicyclic structure; and

n is 0, 1 or 2,

or a pharmacologically acceptable ester or salt thereof; and

a pharmaceutical composition for preventing or treating hypertension or congestive heart failure which comprises the above compound [1] as an active ingredient.

EFFECT OF THE INVENTION

According to the present invention, there is provided 4-aminoquinolines which have

high activity to hypertension or congestive heart failure, are well absorbed into the body upon administration and have long-lasting action as well as a composition for preventing or treating hypertension or congestive heart failure.

The carbon atom content of the carbon containing moieties is indicated by a prefix "C_i-C_j" wherein i is the lowest number of carbon atoms and j is the highest number of carbon atoms.

As the lower alkyl group represented by R^1 and R^2 in the general formula [1], there are an alkyl group having from 1 to 8 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isoamyl, n-hexyl, n-heptyl, n-octyl and the like. As the lower alkenyl group, there are vinyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl and the like. As the lower alkynyl group, there are an acetylene group, 1-propynyl, 2-propynyl, 1-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 1-heptynyl, 1-octynyl and the like. When Y is an alkali metal salt of the 1H-tetrazol-5-yl group in the compound represented by the general formula [1], examples of the alkali metal salt are sodium, potassium etc. Examples of R^5 in the $-CO_2R^5$ group are a hydrogen atom, an alkali metal atom, a lower alkyl group. Examples of the alkali metal salt are sodium, potassium salt etc. Examples of the lower alkyl group are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isoamyl, n-hexyl, n-heptyl, n-octyl and the like. Examples of NR'R" in the -CONR'R" group are amino, methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, di(n-propyl)amino, diisopropylamino, dibutylamino, pyrrolidyl, piperazino, morpholino etc. And examples of R^6 in the $-CONHSO_2R^6$ group are mehtyl, ethyl, n-propyl, n-butyl, isobutyl, t-butyl, cyclopentyl, cyclohexyl, phenyl etc.

When R^3 or R^4 in the general formula [1] represents the lower alkyl group, exmaples of them are as described above about R^1 and R^2. Examples of the substituted lower alkyl group are hydroxymethyl, 2-hydroxyethyl, carboxymethyl, 2-carboxyethyl, methoxymethyl, 2-methoxyethyl etc. Examples of the lower alkoxy are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy etc.

Particular examples of compounds represented by the general formula [1] are as follows. The numbers at the left are compound numbers as they appear in the examples.

1) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline,

2) 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]amino-2-methylquinoline,

3) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

4) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethylquinoline,

5) 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

6) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-n-propylquinoline,

7) 2-n-propyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

8) 2-n-butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]aminoquinoline,

9) 2-n-butyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

10) 2-n-pentyl-4-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

11) 2-trifluoromethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

12) 2-(1-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

13) 2-(2-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

14) 2-(2-propynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

15) 2-(2-butenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

16) 2-(2-butynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

17) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2,8-dimethylquinoline,

18) 2,8-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

19) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-8-methoxy-2-methylquinoline,

20) 8-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)methyl]aminoquinoline,

21) 8-ethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

22) 2-methyl-8-n-propyl-4-[(2'-(tetrazol-5-yl)methyl]aminoquinoline,

23) 2-methyl-8-isopropyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

24) 4-[2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-5-dimethylaminosulfonylquinoline,

25) 2-methyl-5-dimethylaminosulfonyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

26) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-5-morpholinosulfonylquinoline,

27) 2-methyl-5-morpholinosulfonyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

28) 2-methyl-5-piperidinosulfonyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

29) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-6-cyano-2-methylquinoline,

30) 6-cyano-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

31) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline-6-carboxylic acid,

32) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylic acid,

33) 6-carbamoyl-4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline,

34) 6-carbamoyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

35) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-6-(tetrazol-5-yl) quinoline,

36) 2-methyl-6-(tetrazol-5-yl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

37) 6-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

38) 4-[(2'-(N-methanesulfonyl)carbamoylbiphenyl-4-yl)methyl]amino-2-methylquinoline,

39) 2,7,8-trimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

40) 8-trifluoromethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline.

41) ethyl 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethylquinoline-6-carboxylate,

42) ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylate,

43) 2,3-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

44) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

45) 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

46) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

47) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethyl-1,5-naphthyridine,

48) 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

49) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-n-propyl-1,5-naphthyridine,

50) 2-n-propyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

51) 2-n-butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]amino-1,5-naphthyridine,

52) 2-n-butyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

53) 2-n-pentyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

54) 2-trifluoromethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

55) 2-(1-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

56) 2-(2-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

57) 2-(2-propynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

58) 2-(2-butenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

59) 2-(2-butynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

60) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2,8-dimethyl-1,5-naphthyridine,

61) 2,8-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

62) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-8-methyoxy-2-methyl-1,5-naphthyridine,

63) 8-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)methyl]amino-1,5-naphthyridine,

64) 8-ethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

65) 2-methyl-8-n-propyl-4-[(2'-(tetrazol-5-yl)methyl]amino-1,5-naphthyridine,

66) 2-methyl-8-isopropyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

67) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-6-cyano-2-methyl-1,5-naphthyridne,

68) 6-cyano-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

69) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine-6-carboxylic acid,

70) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine-6-carboxylic acid,

71) 6-carbamoyl-4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

72) 6-carbamoyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

73) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-6-(tetrazol-5-yl)-1,5-naphthyridine,

74) 2-methyl-6-(tetrazol-5-yl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

75) 6-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

76) 4-[(2'-(N-methanesulfonyl)carbamoylbiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

77) 2,7,8-trimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

78) 8-trifluoromethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

79) ethyl 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethyl-1,5-naphthyridine-6-carboxylate,

80) ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine-6-carboxylate,

81) 2,3-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

82) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,7-naphthyridine,

83) 6-methyl-8-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-pyrido[2,3-d]pyrimidine,

84) 6-methyl-8-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-pyrido[2,3-b]pyrazine,

85) 2-methyl-4-[2'-(tetrazol-5-yl)biphenyl-4-yl]aminoquinoline,

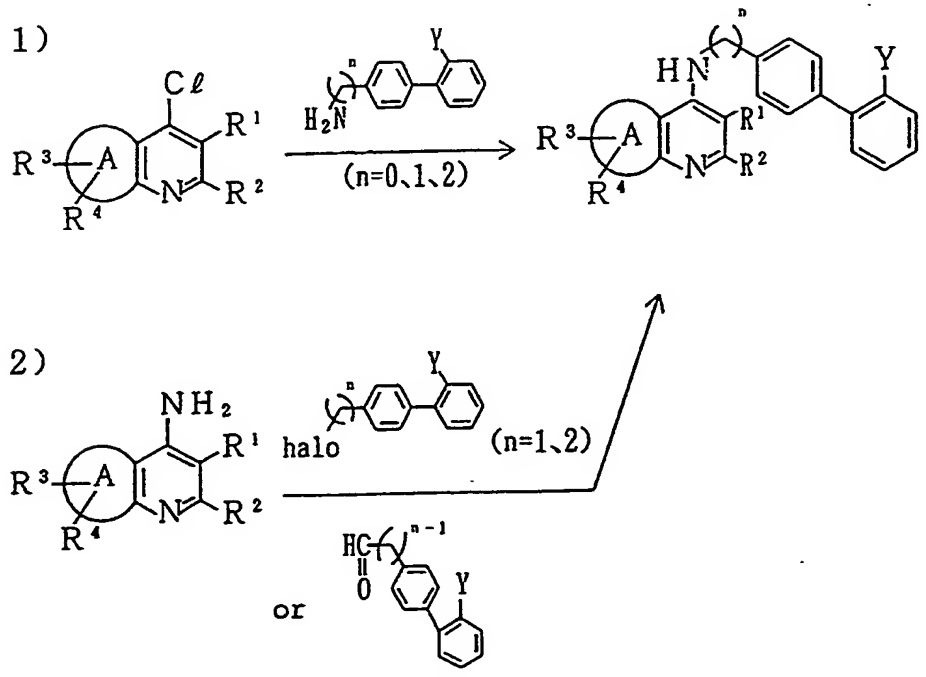
86) 2-ethyl-4-[2'-(tetrazol-5-yl)biphenyl-4-yl]aminoquinoline.

4-Aminoquinolines of the present invention can form a pharmacologically acceptable ester at a part of R^3, R^4 or Y in the general formula [1]. Examples of such an ester are methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl or t-butoxycarbonyl.

Further, 4-aminoquinolines of the present invention can form a salt such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, acetate, propionate, lactate, maleate, lamate, succinate, tartrate and the like at a part of amino group at 4-position. And whem Y is the 1H-tetrazol-5-yl group, they can form an salt such as sodium salt, potassium salt

and the like. In both of cases, these salts may be in the form of a hydrate.

4-Aminoquinolines represented by the general formula [1] can be prepared, for example, according to the following scheme.



A represents a pyridine-fused ring with phenyl, pyridine, pyridazine, pyrimidine or pyrazine ring.

That is, three methods can be exemplified: 1) a method for reacting 4-chloroquinoline and biphenylamine at heating according to the procedure described in EP-387821; 2) a method for alkylating 4-aminoquinolines with biphenyl halide under basic condition, or reductive

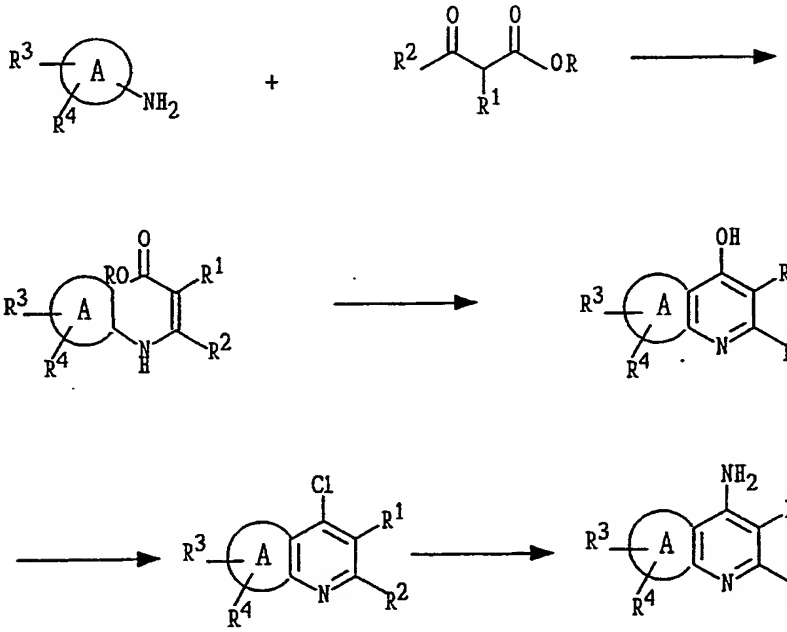
aminating 4-aminoquinolines and biphenylaldehyde under the presence of a reducing agent such as sodium borohydride etc.; 3) a method for acylating 4-aminoquinolines, alkylating them under basic condition, then deacylating them.

In the method 1), biphenylamine is used in a range of from equal to 10-fold mole equivalent amount relative to 4-chloroquinoline and the reaction tempertaure is usually in a range of from 60 °C to 160 °C. In the method 2), as a base which is used for the reaction between 4-aminoquinolines and biphenyl halide, there are lithium amide, sodium amide, potassium amide, n-butyllithium, potassium-t-butoxide which are used for the conventional amination reaction. The reaction temperature is usually in a range of from room temperature to 100 °C depending upon a base and reaction solvent to be used. For example, when reaction is carried out using n-butyllithium in an ethereal solvent such as tetrahydrofuran or an aromatic hydrocarbon solvent such as toluene, room temperature is sufficient. when reaction is carried out using sodium amide etc. in an aromatic hydrocarbon solvent, reaction with 4-aminoquinoline is carried out under heating at reflux, and after that the temperature is lowered to from room temperature to 60 °C and then biphenyl halide is reacted. A base is usually used in a range of from equal to 1.5-fold mole equivalent amount relative to 4-aminoquinoline and biphenyl halide is preferably used in a range of from 0.8 to 1.5-fold mole equivalent amount to 4-aminoquinolines. It is usually preferable that reductive aminating reaction between 4-aminoquinolines and biphenyl halide is carried out at a temperature of from room temperature to 80 °C using from equal to 2-fold mole amount of aminoquinolines relative to the aldehyde. As a reducing agent, sodium borohydride or sodium cyanoborohydride is generally used, and the amount to be used is preferably 1 to 2-fold relative to the theoretical one depending upon an effective amount of hydrogen contained in the reducing agent. As a reaction solvent, alcohols such as methanol, ethanol, propanol etc. and ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran etc. can be used.

In the method 3), acylating of 4-aminoquinolines is advantageous in that the yield of condensation reaction with biphenyl halide is increased due to activation of an amino group by an adjacent carbonyl group. Preferable acylating agents are such that they give R^7 which is a lower alkyl group, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl etc. or a lower alkoxy, for exmple, methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy or t-butoxy. That is, examples of an acylating agent are a lower alkyl-carboxyl chloride such as acetyl chloride, propionyl chloride etc., a lower alkyl-carboxylic anhydride such as acetic anhydride, propionic anhydride etc., a chloride of a carbonic acid ester such as methyl chlorocarbonate, ethyl chlorocarbonate, propyl chlorocarbonate etc., and an anhydride of a carbonic acid ester such as di-t-butyl dicarbonate. An acylation reaction may be carried out using 1.0 to 1.5-fold mole equivalent amount of an acylating agent relative to 4-aminoquinolines in the presence of an

amine such as triethylamine, tributylamine, pyridine etc. as the conventional method. A reaction between acylated 4-aminoquinolines and biphenyl halide is carried out as described above. When R^7 is a lower alkyl group, a deacylation reaction can be easily carried out, for example, by reaction with lithium aluminum hydride in an ethereal solvent such as diethyl ether, tetrahydrofuran etc. And, when R^7 is a lower alkoxy group, the reaction can be carried out, for example, by heating at a temperature from room temperature to 80 °C in a halogenated hydrocarbon solvent in the presence of an acid catalyst such as hydrochloric acid, sulfuric acid, trifluoroacetic acid etc.

Synthesis of 4-chloroquinolines or 4-aminoquinolines as a starting material can be carried out according to the following scheme.



A represents a phenyl, pyridine, pyridazine, pyrimidine or pyrazine ring.

That is, 4-hydroxyquinolines can be easily obtained by reacting β-keto ester and a substituted aniline, aminopyridine, aminopyridazine, aminopyrimidine or aminopyrazine, according to the method described in Org. Synth. Coll., Vol. 3, page 374, to obtain β-arylaminocrotonate which is heated according to the method described in Org. Synth. Coll., Vol. 3, page 593. The 4-hydroxyquinolines can be easily converted into the corresponding 4-chloroquinolines by the conventional halogenating method, for example, only by treating with phosphorus oxychloride, triphenylphosphine dichloride, triphenylphosphine-carbon tetrachloride. 4-Aminoquinolines can be synthesized by heating 4-chloroquinolines with ammonia, ammonium carbonate, ammonium acetate etc.

Next, the method of pharmacological activity test is described.

1) In vitro angiotensin II mesenteric artery receptor binding assay

According to the method (1) by Gunther et al., a membrane fraction was prepared from mesenteric artery of male rat, 50 μg protein equivalent of it and 0.2 nM ^{125}I-Ang II as well as various concentrations of test compounds were incubated at 22 °C for 90 min. in 200 μl reaction volume of incubation buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM $MgCl_2$, 0.25 % bovine serum albumin, pH 7.2). This was cooled, and the reaction was stopped by addition of ice-cooled phosphate buffer (10 mM phosphate, 140 mM NaCl, pH 7.4, hereinafter referred to as PBS), and then the reaction solution was filtered through a glass fiber filter (Whatman CF/B), the filter was washed, dried, and then the radioactivity of captured ^{125}I-angiotensin II which bound to the receptor was measured by γ-counter. Non-specific bound amount was obtained from the reaction under the presence of 1 μM of unlabeled angiotensin II. The test compound was tested at the concentration of 0.01 to 1 μM, and those that inhibited more than 50 % of total specific bound amount at 1 μM was determined as an active compound, and 50 % inhibiting concentration (IC_{50}) was obtained [see Gunther, S., Gimbrone, M.A. and Alexander, R.W., Circ. Res., 17:278-286, 1980].

2) In vitro adrenal cortex angiotensin II rceptor binding assay

According to the method by Capponi et al. (1), angiotensin II receptor binding assay was carried out by preparing a membrane fraction from an adrenal cortex of a male rat and using this as a receptor material in the same manner as in the above-described pharmacological test 1) [see Capponi, A. M. and Catt, K., J. Biol. Chem. 254:5120-5127(1979)].

3) Antagonism to angiotensin II constriction in an isolated rabbit thoracic aorta

A rectangular strip-like sample of thoracic aorta isolated from an anaethetized rabbit was prepared, and this was suspended at 2.0 g of loaded tension in a Magnus tube filled with Krebs-Henseleitoid nutrition solution which was well aerated with 95 % O_2-5 % CO_2, and the constriction tension was measured using an isometric transducer. After the tension of the sample at rest became stable, accumulative administration of angiotensin II was carried out to obtain a concentration-action curve. Thereafter, the sample was washed with the same nutrition solution, then 10^{-6} M test compound was treated for 20 min. to obtain again a concentration-action curve of angiotensin II. The results were obtained as followed: generated maximum tension at the first accumulative administration of angiotensin II was regarded as 100 %, and the 50 % effective concentration (ED_{50}) was obtained in the presence or absence of the test compound, and pA_2 value was calculated according to the following equations:

$pA_2 = -\log K_B$ $\quad K_B = C/\{(A'/A)-1\}$

C; concentration of the test compound (M)

A'; ED_{50} in the presence of test compound (M)

A; ED_{50} in the absence of the test compound (M)

4) Antagonism to blood pressure increasing by angiotensin II in a spine destroyed rat

Wistar rat anaesthetized with pentobarbital was fixed at dorsal position, and a cannula for measuring blood pressure was inserted into sinister arteria carotis communis, and a cannula for administration of the test compound into dexter external jugular vein and a cannula for administration of angiotensin II into sinister external jugular vein, ambilateral nervus vagus was cut, and artificial respiration was carried out. A thin bar made of metal was stabbed into spinal column through sininster orbita to destroy spine. Blood pressure was recorded on polygraph via pressure transducer from an arterial cannula. After blood pressure was stable for more than 30 min., 3μg/kg of angiotensin II was administered intravenously four times every 15 min., and every 5 min. before the administration of angiotensin II from the second admininstration onward, a solvent, a lower dose of the test compound, and a higher dose of the test compound were admininstered intravenously in this order to observe the blood pressure increasing response by angiotensin II. ED_{50} values were calculated from the inhibiting rate when the first blood pressure increase by angiotensin II was regarded as 100 %.

In the above tests, for example, compound No. 1 shows $IC_{50}=7.8x10^{-7}$ M, indicating that the compound is effective as an agent for preventing or treating hypertension or congestive heart failure.

4-Aminoquinolines or pharmacologically acceptable esters or salts thereof can be formulated, by a conventional method, into a unit dosage form such as tablets, capsules, pills, powders, granules, powder packet, cachets, sterile parenteral solutions or suspensions, eyedrops, solutions or suspensions, elixirs, suppositories, aerosols and emulsions which contains them in a predetermined amount.

For oral admininstration, solid or fluid unit dosage form can be prepared. For preparing solid composition, the active compound is mixed with an excipient or a carrier such as magnesium stearate, dicalcium phosphate, magnesium alminum silicate, calcium sulphate, starch, lactose, acacia, methyl cellulose and the like. A capsule agent is prepared by mixing the compound of the present invention with an inert pharmaceutical excipient, filling the mixture into a hard gelatin capsule having suitable size. A soft gelatin capsule is prepared by machine capsulation of slurry composed of the compound, suitable vegetable oil, light petrolatum or other inert oil.

For preparing a fluid composition, the compound of the present invention is dissolved in aqueous vehicle together with sugar, aromatic flavor and preservative to obtain a syrup. Elixirs are prepared using an alcoholic vehicle such as ethanol, a sweetener such as sugar and saccharin as well as a flavor. Suspensions are prepared using a suspending agent such as acacia, tragacanth or methyl cellulose and an aqueous vehicle.

For parenteral administration, a fluid unit dosage form is prepared using the compound

of the present invention and a sterile vehicle. Depending upon a vehicle such as water, Ringer's solution, isotonic sodium chloride solution and the concentration to be used, the compound is suspended or dissolved in the vehicle. For preparing solutions, the compound is dissolved in water for injection, and this is sterile filtered, filled into a vial or an ampoule, and sealed. Advantageously, an adjuvant such as local anaesthetic, preservative and buffer is dissolved in vehicle. Alternatively, a lyophilized powder having good shelf stability can be prepared. In the case of this formulation, the powder is reconstituted upon use. Parenteral suspensions can be similarly prepared using the compound of the present invention. In the case of this formulation, the compound of the present invention can be sterilized by exposure to ethylene oxide before suspended in a sterile vehicle. Advantageously, a surfactant or a wetting agent is added to facilitate dispersion of the compound.

Alternatively, the compound of the present invention can be formulated into a local dosage form in combination with a suitable carrier for local administration. Examples of a carrier to be used are cream, ointment, lotion, paste, jelly, spray, aerosol and the like. Further, when other form can not be administered, suppositories can be prepared. Examples of a base are cacao butter, polyethylene glycol, polyethylene sorbitan monostearate and the like.

4-Aminoquinolines or pharmacologically acceptable esters or salts thereof are administered orally, parenterally, by insufflation, rectally, or locally. Parenteral administration includes subcutaneous, intravenous, intramuscular, intranasal administration or injection. Dose to be administered to an adult is in a range of 1 to 50 mg/day. The exact dose can be selected from the above range, taking the age of the patient, the weight, condition and route of administration into consideration. Such factors are well known to an ordinary skilled physician or pharmacist. The frequency of administration is usually from one to four times a day.

Additionally, no toxicity of the compounds of the present invention or pharmacologically acceptable esters or salts thereof was observed in the above-described dose range.

DESCRIPTION OF THE PREFERED EMBODIMENTS

The following Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

EXAMPLE 1

Preparation of 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline (compound No.1)

Method A)

50 Mg (0.31 mmol) of 4-aminoquinaldine was dissolved in 0.4 ml of tetrahydrofuran, and 220 μl of 1.59 mol/l n-butyllithium/hexane solution was added dropwise at 0 °C, and then the solution was stirred for 30 min. 120 Mg (0.346 mmol) of (2'-t-butoxycarbonylbiphenyl-4-yl)methyl bromide was dissolved in 0.2 ml of tetrahydrofuran, and the solution was added

dropwise into the reaction solution, and stirred at room temperature for 24 hours. After tetrahydrofuran was distilled off under the reduced pressure, the residue was diluted with water, and extracted with chloroform. The chloroform layer was washed with an aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulphate. The solvent was distilled off under the reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH=10:1-5:1) to obtain 32 mg of 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]aminoquinaldine. 97Mg (0.228 mmol) of 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]aminoquinaldine was dissolved in 1 ml of chloroform, and 1 ml of trifluoroacetic acid was added to heat at reflux for 2 hours. Trifluoroacetic acid and chloroform were distilled off under the reduced pressure, and the residue was recrystallized to obtain 4-[(2'-carboxybiphenyl-4-yl)methyl]aminoquinaldine as 11 mg of trifluoroacetate of a white needle. This has the following NMR spectrum.

δppm($CDCl_3$): 2.66 (3H,s), 4.85 (2H), 6.71 (1H,s), 7.34-8.42 (12H,m)

Method B)

500 Mg of 4-aminoquinaldine was heated at reflux for 2 hours together with 130 mg of sodium amide in 20 ml of toluene and this was allowed to cool, and 300 mg of [(2'-t-butoxycarbonylbiphenyl-4-yl)methyl bromide was added to heat again at reflux for 5 hours, and the similar treatment was carried out to obtain 226 mg of 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]aminoquinaldine. This has the following NMR spectrum.

δppm($CDCl_3$): 1.28 (9H,s), 2.60 (3H,s), 4.59 (2H,d,J=4.9Hz), 5.38 (1H,bt), 6.41 (1H,s), 7.3-7.6 (8H,m), 7.63(1H,t,J=7Hz), 7.74 (1H,d,J=8Hz), 7.80 (1H,d,J=7Hz), 7.95 (1H,d,J=8Hz)

This was derived into compound No. 1 by the similar treatment as in the method A.

Method C)

1.5 G (9.48 mmol) of 4-aminoquinaldine, 1.07 ml (11.34 mmol) of acetic anhydride, 1.59 ml (11.41 mmol) of triethylamine were dissolved in 3ml of dichloromethane, and stirred at room temperature for 12 hours. After the reaction solution was diluted with dichloromethane, the solution was washed with an aqueous saturated sodium bicarbonate solution, and dried over sodium sulphate. The solvent was distilled off under the reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to obtain 1.04 g of 4-acetylaminoquinaldine (yield 55%). This has the following NMR spectrum.

δppm ($CDCl_3$): 2.32 (3H,s), 2.68 (3H,s), 7.43 (1H,m), 7.65 (1H,m), 7.81 (1H,d,J=8.4Hz), 8.00 (1H,d,J=8.7Hz), 8.09 (1H,bs), 8.27 (1H,bs)

465 Mg (2.32 mmol) of the acetylamino compound was dissolved in 3 ml of dimethylformamide, and 110 mg (2.75 mmol) of 60% oily sodium hydride was added portionwise while stirring. The mixture was stirred at room temperaure for 10 minutes, heated

to 60°C, and then a solution of 1.2 g (3.46 mmol) of (2'-t-butoxycarbonylbiphenyl-4-yl)methyl bromide in 3 ml of dimethylformamide was added. After reaction at 60°C for 12 hours, the solvent was distilled off under the reduced pressure, the residue was diluted with dichloromethane, washed with water, dried over sodium sulphate, and then the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to obtain 875 mg of N-acetyl-4-[(2'-butoxycarbonylbiphenyl-4-yl)methyl]amino-2-methylquinoline as white amorphous powder (yield 81%). This has the following NMR spectrum.

δppm ($CDCl_3$): 1.26 (9H,s), 1.83 (3H,s), 2.68 (3H,s), 4.39 (1H,d,J=14.3Hz), 5.61 (1H,d,J=14.3Hz), 6.87 (1H,s), 7.23 (4H,s), 7.26-7.58 (4H), 7.72-7.78 (3H), 8.10 (1H,d,J=9.2Hz)

690 Mg (1.48 mmol) of the N-acetyl compound was dissolved in 10 ml of diethyl ether, and 60 mg (1.58 mmol) of lithium alminum hydride was added portionwise while stirring. After reaction at room temperature for 12 hours, methanol was added to treat the excess reagent, 1N-sodium hydroxide was added, and then extracted with dichloromethane. The extract was dried over sodium sulphate, the solvent was distilled off under the reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate) to obtain 244 mg of 4-[(2'-butoxycarbonylbiphenyl-4-yl)methyl]aminoquinaldine as white amorphous powder (yield 39%). This was converted into compound No. 1 by the similar method as in the method A.

EXAMPLE 2

Preparation of 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No.3)

500 Mg of 4-aminoquinaldine, 0.70 g of di-t-butyl dicarbonate and 0.34 g of trimethylamine in a mixture of 10 ml of tetrahydrofuran and 3 ml of dimethylformamide were heated at reflux for 16 hours. After cooling, the reaction mixture was concentrated, the residue was purified by silica gel column chromatography (chloroform:methanol=80:1) to obtain 353 mg of 4-N-t-butoxycarbonylaminoquinaldine. This has the following NMR spectrum.

δppm ($CDCl_3$): 1.58 (9H,s), 2.71 (3H,s), 7.31 (1H,bs), 7.48 (1H,t), 7.67 (1H,t), 7.75 (1H,d,J=8,4Hz), 8.02 (1H,d), 8.04 (1H,s)

To a solution of 353 mg of the aminoquinaldine in 3 ml of dimethylformamide was added 65 mg of 60% oily sodium hydride at room temperature. After evolution of hydrogen gas ceased, a solution of 0.82 g of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide in 4 ml of dimethylformamide was added dropwise, and further stirred at room temperature for 40 minutes. To the reaction mixture was added an aqueous saturated ammonium chloride solution, and the mixture was extracted with ethyl acetate, washed with

water, and dried over sodium sulphate. The solvent was distilled off under the reduced pressure, the residue was purified by silica gel column chromatography (chloroform) to obtain 0.50 g of 4-N-t-butoxycarbonyl-N-[(2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]amino-2-methylquinoline. This has the following NMR spectrum.

δppm ($CDCl_3$): 1.33 (9H,s), 2.58 (3H,s), 4.44 (1H,d,J=14.6Hz), 5.12 (1H,d,J=14.3Hz), 6.8-7.7 (26H,m), 7.86 (1H,d,J=7.3Hz), 8.03 (1H,d,J=8.4Hz)

395 Mg of the product was dissolved in 5 ml of chloroform, and 1 ml of trifluoroacetic acid was added to stir for 2 hours, the reaction solution was concentrated under the reduced pressure to remove trifluoroacetic acid. The residue was dissolved in chloroform, and triethylamine was added to neutralize. The solvent was distilled off, and the residue was purified by silica gel column chromatography (chloroform:methanol=30:1-20:1) to obtain 4-[(2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinaldine. This has the following NMR spectrum.

δppm ($CDCl_3$): 2.59 (3H,s), 4.35 (2H,d,J=4.9Hz), 4.97 (1H,bs), 6.37 (1H,s), 6.8-8.1 (27H,m)

27 Mg of the product was stirred at room temperature for 1 hour in 2ml of methanol in the presence of 0.1 ml of 10% hydrochloric acid. The reaction solution was dried to solidify under the reduced pressure, and the solid was washed with diethyl ether, the residue was dissolved in a small amount of methanol, and diethyl ether was added again to crystallize. The crystal was filtered, and this was washed with ether, dried to obtain 18 mg of hydrochloride of 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No.3). This has the following NMR spectrum.

δppm ($CDCl_3$): 2.74 (3H,s), 4.9 (2H), 6.68 (1H,s), 7.2-8.1 (12H,m), 8.49 (1H,d,J=7.8Hz)

EXAMPLE 3

Preparation of 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No.5)

4-Amino-2-ethylquinoline was prepared from aniline and ethyl propionylacetate according to the method described in Nihonkagakuzasshi, Vol.86, page 1192. This has the following NMR spectrum.

^1H NMR δppm ($CDCl_3$) 1.35 (3H,t,J=7.7Hz), 2.85 (2H,q,J=7.7Hz), 4.73 (2H,broad s), 6.53 (1H,s), 7.40 (1H,m), 7.62 (1H,m), 7.73 (1H,dd,J=8.2Hz, 0.9Hz), 7.96 (1H,d,J=9.2Hz)

500 Mg of 4-amino-2-ethylquinoline, 0.8 ml of di-t-butyl dicarbonate and 0.49 ml of triethylamine were dissolved in a mixed solvent of 10 ml of tetrahydrofuran and 3 ml of dimethylformamide, and this solution was heated at reflux for 16 hours. The reaction solution was concentrated under the reduced pressure, the residue was purified by silica gel column

chromatography [chloroform-methanol (100:1)] to obtain 250 mg of 4-N-t-butoxycarbonylamino-2-ethylquinoline as white solid material. This has the following NMR spectrum.

^{1}H-NMR δppm ($CDCl_3$) 1.40 (3H,t,J=7.8Hz), 1.57 (9H,s), 2.97 (2H,q,J=7.8Hz), 7.45 (1H,m), 7.65 (1H,m), 7.79 (1H,d,J=8.1Hz), 8.04 (1H,d,J=8.6Hz), 8.06 (1H,s)

250 Mg of 4-N-t-butoxycarbonylamino-2-ethylquinoline and 609 mg of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 3 ml of dimethylformamide, and 44 mg of 60% sodium hydride was added while stirring this solution at room temperature. After evolution of hydrogen gas ceased, this was heated to 50°C for 20 hours. The solvent was distilled off under the reduced pressure, the residue was dissolved in dichloromethane, and washed with water. The aqueous layer was further extracted with dichloromethane. After the organic layer was dried over sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography [chloroform-methanol (100:1)] to obtain 568 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-ethylquinoline as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.23 (3H,t,J=7.8Hz), 1.32 (9H,s), 2.85 (2H,q,J=7.8Hz), 4.35 (1H,broad d), 5.15 (1H,broad d), 6.91 (6H,m), 6.98 (2H,d,J=8.4Hz), 7.03 (2H,d,J=8,4Hz), 7.15-7.55 (14H), 7.63-7.73 (2H), 7.87 (1H,m), 8.06 (1H,d,J=8.1Hz)

To a solution of 568 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-ethylquinoline in 5 ml of chloroform was added 1 ml of trifluoroacetic acid, and the solution was stirred at room temperature for 3 hours. After the solvent and trifluoroacetic acid were distilled off under the reduced pressure, the residue was dissolved again in 5 ml of chloroform, 1 ml of triethylamine was added, and stirred at room temperature for 1 hour. After the solvent was distilled off under the reduced pressure, the residue was purified by silica gel column chromatography [chloroform-methanol (10:1)] to obtain 390 mg of 2-ethyl-4-[(2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.31 (3H,t,J=7.8Hz), 2.81 (2H,q,J=7.8Hz), 4.37 (2H,d,J=4.9Hz), 6.34 (1H,s), 6.92 (6H,m), 7.1-7.6 (19H), 7.9-8.0 (2H)

390 Mg of 2-ethyl-4-[(2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline was dissolved in 10 ml of methanol, 1 ml of 2N HCl was added, and stirred at room temperature for 2 hours. The reaction solution was dried to solidify, the solid was scrapered into powder by spatula, and the powder was washed with ethyl ether. After that, the powder was crystallized from a mixed solution of methanol-ethyl ether, and this was further washed with ethyl ether, dried to obtain 100 mg of hydrochloride of 2-ethyl-4-[(2'-(tetrazol-5-

yl)biphenyl-4-yl)methyl]aminoquinoline. This has the following NMR spectrum.

^{1}H NMR δppm (CD_3OD) 1.36 (3H,t,J=7.8Hz), 2.91 (2H,q,J=7.8Hz), 6.57 (1H,s), 7.16 (2H,d,J=8.4Hz), 7.37 (2H,d,J=8.4Hz), 7.53-7.96 (7H), 8.38 (1H,d,J=7.8Hz)

EXAMPLE 4

Preparation of 2-n-propyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No. 7)

4-Amino-2-propylquinoline was prepared from aniline and ethyl butyrylacetate according to the method described in Nihonkagakuzasshi, Vol. 86, page 1192. This has the following NMR spectrum.

^{1}NMR δppm ($CDCl_3$) 1.00 (3H,t,J=7.7Hz), 1.80 (2H,m), 2.79 (2H,m), 4.70 (2H,broad s), 6.52 (1H,s), 7.39 (1H,m), 7.61 (1H,m), 7.72 (1H,dd,J=8.2Hz, 0.9Hz), 7.96 (1H,d,J=7.8Hz)

500 Mg of 4-amino-2-propylquinoline, 0.86 ml of di-t-butyl dicarbonate and 164 mg of 4-dimethylaminopyridine were dissolved in 5 ml of pyridine, and this solution was heated to 50°C for 3 hours. The reaction solution was concentrated under the reduced pressure, the residue was purified by silica gel column chromatography (chloroform) to obtain 725 mg of 4-N-t-butoxycarbonylamino-2-propylquinoline as pale yellow solid material. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.03 (3H,t,J=7.2Hz), 1.59 (9H,s), 1.86 (2H,m), 2.92 (2H,m), 7.48 (1H,m), 7.67 (1H,m), 7.74 (1H,d,J=8.9Hz), 8.05 (1H,s), 8.05 (1H,d,J=7.8Hz)

715 Mg of 4-N-t-butoxycarbonylamino-2-propylquinoline and 1.67 g of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 10 ml of dimethylformamide, and 120 mg of 60% oily sodium hydride was added while stirring this solution at room temperature. After evolution of hydrogen gas ceased, this was heated to 50°C for 20 hours. The solvent was distilled off under the reduced pressure, the residue was dissolved in dichloromethane, and washed with water. The aqueous layer was further extracted with dichloromethane. After the organic layer was dried over sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to obtain 1.2 g of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-propylquinoline as pale yellow amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm($CDCl_3$) 0.89 (3H,t,J=7.3Hz), 1.31 (9H,s), 1.68 (2H,m), 2.81 (2H,t,J=7.6Hz), 4.34 (1H,broad d), 5.17 (1H,broad d), 6.90 (6H,m), 6.96 (2H,d,J=8.4Hz), 7.02 (2H,d,J=8.4Hz), 7.1-7.6 (14H), 7.62-7.73 (2H), 7.87 (1H,m), 8.06 (1H,d,J=8.6Hz)

2 Ml of trifluoroacetic acid was added to a solution of 1.2 g of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-propylquinoline in 10 ml of

chloroform, and the solution was stirred at room temperature for 20 hours. After the solvent and trifluoroacetic acid were distilled off under the reduced pressure, the residue was dissolved again in dichloromethane, and washed with an aqueous saturated $NaHCO_3$ solution. The aqueous layer was further extracted with dichloromethane. The organic layer was dried over sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (chloroform-methanol (20:1)] to obtain 198 mg of 2-propyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline as pale yellow solid material. This has the following NMR spectrum.

^{1}H NMR δppm($CDCl_3$) 0.78 (3H,t,J=7.3Hz), 1.56 (2H,sex,J=7.3Hz), 2.68 (2H,t,J=7.3Hz), 6.85 (1H,s), 6.87 (2H,d,J=8.2Hz), 6.93 (2H,d,J=8.2Hz), 7.32 (1H,d,J=7.6Hz), 7.4-7.6 (4H), 7.65 (1H,m), 7.78 (1H,d,J=7.6Hz), 7.80 (1H,d,J=7.8Hz)

EXAMPLE 5

Preparation of 2,8-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No. 18)

4-Amino-2,8-dimethylquinoline was prepared from o-toluidine and ethyl acetoacetate according to the method described in Nihonkagakuzasshi, Vol. 86, page 1192. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.61 (3H,s), 2.76 (3H,s), 4.59 (2H,broad s), 6.51 (1H,s), 7.28 (1H,dd,J=8.4Hz,7.3Hz), 7.48 (1H,d,J=7.3Hz), 7.56 (1H,d,J=8.4Hz)

300 Mg of 4-amino-2,8-dimethylquinoline, 0.48 ml of di-t-butyl dicarbonate and 100 mg of 4-dimethylaminopyridine were dissolved in 3 ml of pyridine, and this solution was heated to 50°C for 3 hours. The reaction solution was concentrated under the reduced pressure, the residue was purified by silica gel column chromatography (chloroform) to obtain 381 mg of 4-N-t-butoxycarbonylamino-2,8-dimethylquinoline as pale yellow amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.58 (9H,s), 2.72 (3H,s), 2.79 (3H,s), 7.24 (1H,broad s), 7.35 (1H,dd,J=8.1Hz,7.3Hz), 7.52 (1H,d,J=7.3Hz), 7.57 (1H,d,J=8.1Hz), 8.01 (1H,s)

508 Mg of 4-N-t-butoxycarbonylamino-2,8-dimethylquinoline and 1.25 g of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 5 ml of dimethylformamide, and 90 mg of 60% oily sodium hydride was added while stirring this solution. After evolution of hydrogen gas ceased, this was heated to 50°C for 20 hours. The aqueous layer was further extracted by dichloromethane. After the organic layer was dried by sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to obtain 483 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2,8-dimethylquinoline as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.32 (9H,s), 2.59 (3H,s), 2.80 (3H,s), 4.35 (1H,broad d), 5.15 (1H,broad d), 6.92 (6H,m), 6.98 (2H,d,J=8.5Hz), 7.03 (2H,d,J=8.5Hz), 7.15-7.65 (16H), 7.86 (1H,dd,J=7.6Hz, 1.6Hz)

1 Ml of trifluoroacetic acid was added to a solution of 483 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2,8-dimethylquinoline in 5 ml of chloroform, and the solution was stirred at room temperature for 3 hours. After the solvent and trifluoroacetic acid were distilled off under the reduced pressure, the residue was dissolved again in 5 ml of chloroform, 1 ml of triethylamine was added, and stirred at room temperature for 1 hour. After the solvent was distilled off under the reduced pressure, the residue was purified by silica gel column chromatography (chloroform-methanol (10:1)] to obtain 177 mg of 4-[(2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]amino-2,8-dimethylquinoline as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.47 (3H,s), 2.70 (3H,s), 4.41 (2H,d,J=5.4Hz), 5.96(1H,s), 6.91 (6H,m), 7.15-7.5 (18H), 7.86-7.92 (2H)

108 Mg of 4-[(2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl)methyl]amino-2,8-dimethylquinoline was dissolved in 5 ml of methanol, 0.5 ml of 2N HCl was added, and stirred at room temperature for 2 hours. The reaction solution was dried to solidify under the reduced pressure, and the solid was scrapered into powder by spatula, and the powder was washed with ethyl ether. After that, this was crystallized from a mixed solvent of methanol-ethyl ether, further washed with ethyl ether, and dried to obtain 55 mg of hydrochloride of 2,8-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline. This has the following NMR spectrum.

^{1}H NMR δppm (CD_3OD) 2.73 (3H,s), 3.35 (3H,s), 4.80 (2H,s), 6.47 (1H,s), 7.1-7.8 (10H), 8.31 (1H,d,J=8.4Hz)

EXAMPLE 6

Preparation of 2,7,8-trimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No. 39)

4-Amino-2,7,8-trimethylquinoline was prepared from 2,3-dimethylaniline and ethyl acetoacetate according to the method descrined in Nihonkagakuzasshi, Vol. 86, page 1192. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.45 (3H,s), 2.59 (3H,s), 2.72 (3H,s), 4.50 (2H,broad s), 6.43 (1H,s), 7.20 (1H,d,J=8.2Hz), 7.45 (1H,d,J=8.2Hz)

500 Mg of 4-amino-2,7,8-trimethylquinoline, 0.68 ml of di-t-butyl dicarbonate and 164 mg of 4-dimethylaminopyridine were dissolved in 5 ml of pyridine, and this solution was heated to 50°C for 3 hours. The reaction solution was concentrated under the reduced pressure, the residue was purified by silica gel column chromatography (developer: chloroform) to obtain 756 mg of 4-N-t-butoxycarbonylamino-2,7,8-trimethylquinoline as pale yellow solid

material. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.58 (9H,s), 2.47 (3H,s), 2.71 (3H,s), 2.75 (3H,s), 7.21 (1H,broad s), 7.28 (1H,d,J=8.6Hz), 7.47 (1H,d,J=8.6Hz), 7.95 (1H,s)

756 Mg of 4-N-t-butoxycarbonylamino-2,7,8-trimethylquinoline and 1.77 g of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 10 ml of dimethylformamide, and 127 mg of 60 % oily sodium hydride was added while stirring this solution at room temperature. After evolution of hydrogen gas ceased, this was heated to 50°C for 20 hours. The solvent was distilled off under the reduced pressure, the residue was dissolved in dichloromethane and washed with water. The aqueous layer was further extracted with dichloromethane. After the organic layer was dried over sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to obtain 425 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2,7,8-trimethylquinoline as pale yellow amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.32 (9H,s), 2.48 (3H,s), 2.57 (3H,s), 2.75 (3H,s), 4.32 (1H,broad d), 5.13 (1H,broad d), 6.92 (6H,m), 6.98 (2H,d,J=8.8Hz), 7.03 (2H,d,J=8.8Hz), 7.15-7.55 (15H), 7.86 (1H,dd,J=7.7Hz,1.8Hz)

1 Ml of trifluoroacetic acid was added to a solution of 425 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2,7,8-trimethylquinoline in 5 ml of chloroform, and the solution was stirred at room temperature for 20 hours. After the solvent and trifluoroacetic acid were distilled off under the reduced pressure, the residue was dissolved again in dichloromethane, and washed with an aqueous saturated $NaHCO_3$ solution. The aqueous layer was further extracted with dichloromethane. The organic layer was dried by sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography [chloroform-methanol (20:1)] to obtain 102 mg of 2,7,8-trimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline as pale yellow solid material. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.46 (3H,s), 2.64 (3H,s), 2.70 (3H,s), 6.88 (1H,s), 7.02 (2H,d,J=8.1Hz), 7.15 (2H,d,J=8.1Hz), 7.3-7.6 (5H), 7.90 (1H,dd,J=7.6Hz,1.4Hz)

EXAMPLE 7

Preparation of 8-trifluoromethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline (compound No. 40)

4-Amino-8-trifluoromethyl-2-methylqionoline was prepared from 2-trifluoromethylaniline and ethyl acetoacetate according to the method described in Nihonkagakuzasshi, Vol 86, page 1192. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.60 (3H,s), 4.66 (2H,broad s), 6.55 (1H,s), 7.38

(1H,dd,J=8.4Hz,7.3Hz), 7.89 (1H,d,J=8.4Hz), 7.96 (1H,d,J=7.3Hz)

500 Mg of 4-amino-8-trifluoromethyl-2-methylquinoline, 0.56 ml of di-t-butyl dicarbonate and 135 mg of 4-dimethylaminopyridine were dissolved in 5 ml of pyridine, and this solution was heated to 50°C for 3 hours. The reaction solution was concentrated under the reduced pressure, the residue was purified by silica gel column chromatography (chloroform) to obtain 713 mg of 4-N-t-butoxycarbonylamino-8-trifluoromethyl-2-methylquinoline as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.59 (9H,s), 2.74 (3H,s), 7.22 (1H,broad s), 7.50 (1H,t,J=8.4Hz), 7.94 (1H,d,J=8.4Hz), 8.02 (1H,d,J=8.4Hz), 8.09 (1H,s)

700 Mg of 4-N-t-butoxycarbonylamino-8-trifluoromethyl-2-methylquinoline and 1.43 g of [2'-(1-triphenylmethyltetrazol-5-yl)bipheynyl-4-yl]methyl bromide were dissolved in 10 ml of dimethylformamide, and 103 mg of 60% oily sodium hydride was added while stirring this soluiton at room temperature. After evolution of hydrogen gas ceased, this was heated to 50°C to react for 20 hours. The solvent was distilled off under the reduced pressure, the residue was dissolved in dichloromethane, and washed with water. The aqueous layer was further extracted with dichloromethane. After the organic layer was dried over sodium sulphate, the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate (10:1)] to obtain 991 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-8-trifluoromethyl-2-methylquinoline as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR ($CDCl_3$) δppm ($CDCl_3$) 1.31 (9H,s), 2.63 (3H,s), 4.50 (1H,broad d,J=14.9Hz), 5.03 (1H,broad d ,J=14.9Hz), 6.94 (6H,m), 6.99 (2H,d,J=8.4Hz), 7.04 (2H,d,J=8.4Hz), 7.2-7.6 (14H), 7.80-7.88 (2H), 7.98 (1H,d,J=7.3Hz)

1 Ml of trifluoroacetic acid was added to a solution of 980 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-8-trifluoromethyl-2-methylquinoline in 5 ml of chloroform, and the solution was stirred at room temperature for 20 hours. After the solvent and trifluoroacetic acid were distilled off, the residue was dissolved again in dichloromethane, and washed with an aqueous saturated $NaHCO_3$ solution. The aqueous layer was further extracted with dichloromethane. The organic layer was dried over sodium sulphate, and the solvent was distilled off under the reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate (4:1)] to obtain 54 mg of 8-trifluoromethyl-2-methyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline as white solid material. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.62 (3H,s), 4.49 (1H,d,J=4.9Hz), 5.30 (1H,broad t), 6.45 (1H,s), 7.18-7.54 (8H), 7.89-7.98 (3H)

EXAMPLE 8

Preparation of ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylate (compound No. 42)

Ethyl 4-Amino-2-ethylquinoline-6-carboxylate was prepared from ethyl 4-aminobenzoate and ethyl propionylacetate according to the method described in Nihonkagakuzasshi, Vol. 86, page 1192. This has the following NMR spectrum.

^{1}H NMR δppm($CDCl_3$) 1.36 (3H,t,J=7.6Hz), 1.43 (3H,t,J=7.1Hz), 2.86 (2H,q,J=7.6Hz), 4.43 (2H,q,J=7.1Hz), 4.92 (2H,broad s), 6.56 (1H,s), 7.95 (1H,d,J=8.7Hz), 8.21 (1H,dd,J=8.7Hz,2.0Hz), 8.55 (1H,d,J=2.0Hz)

400 Mg of ethyl 4-amino-2-ethylquinoline-6-carboxylate, 0.42 ml of di-t-butyl dicarbonate and 100 mg of 4-dimethylaminopyridine were dissolved in 5 ml of pyridine, and this solution was heated at 50°C for 15 hours. The reaction solution was concentrated under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate-hexane (1:5)] to obtain 310 mg of ethyl 4-N-t-butoxycarbonylamino-2-ethylquinoline-6-carboxylate as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.41 (3H,t,J=7.6Hz), 1.43 (3H,t,J=7.1Hz), 1.58 (9H,s), 2.98 (2H,q,J=7.6Hz), 4.44 (2H,q,J=7.1Hz), 7.68 (1H,broad s), 8.04 (1H,d,J=8.8Hz), 8.13 (1H,s), 8.24 (1H,dd,J=8.8Hz,1.8Hz), 8.64 (1H,d,J=1.8Hz)

310 Mg of ethyl 4-N-t-butoxycarbonylamino-2-ethylquinoline-6-carboxylate and 750 mg of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 3 ml of dimethylformamide, and 54 mg of 60 % oily sodium hydride was added while stirring at room temperature. After evolution of hydrogen gas ceased, the reaction solution was heated to 50°C for 20 hours. The solvent was distilled off under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate-hexane (1:4)] to obtain 646 mg of ethyl 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-ethylquinoline-6-carboxylate as white amorphous powder. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.24 (3H,t,J=7.6Hz), 1.33 (9H,broad s), 1.42 (3H,t,J=7.0Hz), 2.86 (2H,q,J=7.6Hz), 4.43 (3H), 5.17 (1H,broad d), 6.89-7.49 (23H), 7.88 (1H,dd,J=6.8Hz,1.9Hz), 8.08 (1H,d,J=8.7Hz), 8.27 (1H,dd,J=8.7Hz,2.0Hz), 8.45 (1H,d,J=2.0Hz)

635 Mg of ethyl 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-ethylquinoline-6-carboxylate was dissolved in 5 ml of dichloromethane, and 1 ml of trifluoroacetic acid was added to this solution to stir at room temperature for 20 hours. After the excess trifluoroacetic acid was distilled off under the resuced pressure, the residue was dissolved again in dichloromethane, and washed with aqueous ammonia. The aqueous layer was further extracted with dichloromethane. The organic layer was dried over sodium

sulfate, the solvent was distilled off under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate-hexane (4:1)] to obtain 462 mg of ethyl 2-ethyl-4-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylaminoquinoline-6-carboxylate and 63 mg of ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylate (compound No. 42) as pale yellow solid. These have the following spectrum.

ethyl 2-ethyl-4-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylaminoquinoline-6-carboxylate

^{1}H NMR δppm ($CDCl_3$) 1.32 (3H,t,J=7.6Hz), 1.40 (3H,t,J=7.1Hz), 2.82 (2H,q,J=7.6Hz), 4.40 (2H,q,J=7.1Hz), 4.45 (2H,d,J=4.9Hz), 5.49 (1H,broad t), 6.40 (1H,s), 6.92-7.52 (22H), 7.95 (1H,dd,J=7.3Hz,1.6Hz), 7.98 (1H,d,J=8.6Hz), 8.21 (1H,dd,J=8.6Hz,1.4Hz), 8.50 (1H,d,J=1.4Hz)

ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylate (Compound No. 42)

^{1}H NMR δppm ($CDCl_3$) 1.34 (3H,t,J=7.6Hz), 1.42 (3H,t,J=7.1Hz), 2.86 (2H,q,J=7.6Hz), 4.42 (2H,q,J=7.1Hz), 4.55 (2H,d,J=5.4Hz), 5.72 (1H,broad t), 6.43 (1H,s), 7.21 (2H,d,J=7.8Hz), 7.33 (2H,d,J=7.8Hz), 7.44-7.56 (3H), 7.92 (1H,dd,J=8.8Hz,1.9Hz), 7.95 (1H,d,J=8.8Hz), 8.20 (1H,dd,J=8.8Hz,1.6Hz), 8.55 (1H,d,J=1.6Hz)

EXAMPLE 9

Preparation of 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine (Compound No. 46)

430 Mg of 4-chloro-2-methyl-1,5-naphthyridine prepared according to the method described in J.Royal Netherlands Chem. Soc., 95, 220 (1976) and 5 ml of phenol were heated to 180°C. Heating was continued for another 2 hours while ammonia gas was blowing into this solution. The temperature was lowered to about 100°C, the phenol was distilled off under the reduced pressure, the residue was dissolved in dichloromethane and washed with 2 N NaOH. The aqueous layer was further extracted with dichloromethane, the combined organic layer was dried over sodium sulfate, and the solvent was distilled off under the reduced pressure to obtain 390 mg of 4-amino-2-methyl-1,5-naphthyridine as pale brown solid. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.59 (3H,s), 5.53 (2H,broad s), 6.63 (1H,s), 7.53 (1H,dd,J=8.4Hz,4.2Hz), 8.16 (1H,dd,J=8.4Hz,1.6Hz), 8.68 (1H,dd,J=4.2Hz,1.6Hz)

390 Mg of 4-amino-2-methyl-1,5-naphthyridine, 0.84 ml of di-t-butyl dicarbonate and 150 mg of 4-dimethylaminopyridine were dissolved in 5 ml of pyridine, and this solution was heated to 50°C for 12 hours. The reaction solution was concentrated under the reduced pressure, and the resulting crude product was purified by silica gel column chromatpgraphy

[ethyl acetate] to obtain 413 mg of 4-N-t-butoxycarbonylamino-2-methyl-1,5-naphthyridine as pale yellow solid. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.59 (9H,s), 2.73 (3H,s), 7.61 (1H,dd,J=8.4Hz,4.3Hz), 8.18 (1H,s), 8.26 (1H,dd,J=8.4Hz,1.6Hz), 8.75 (1H,dd,J=4.3Hz,1.6Hz), 9.03 (1H,broad s)

630 Mg of 4-N-t-butoxycarbonylamino-2-methyl-1,5-naphthyridine and 2 g of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 5 ml of dimethylformamide, and 146 mg of 60 % oily sodium hydride was added while stirring at room temperature. After evolution of hydrogen gas ceased, the reaction temperature was heated to 50°C, and stirring was continued for 20 hours. The solvent was distilled off under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate-hexane (1:1)] to obtain 1.73 g of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-methyl-1,5-naphthyridine as pale yellow amorphous solid. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.35 (9H,s), 2.57 (3H,s), 4.98 (2H,s), 6.90-7.52 (22H), 7.10 (1H,s), 7.61 (1H,dd,J=8.5Hz,4.2Hz), 7.85 (1H,dd,J=6.8Hz,1.9Hz), 8.30 (1H,dd,J=8.5Hz,1.8Hz), 8.94 (1H,dd,J=4.2Hz,1.8Hz)

1.71 G of 4-N-t-butoxycabonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-methyl-1,5-naphthyridine was dissolved in 10 ml of dichloromethane, and 2 ml of trifluoroacetic acid was added to stir at room temperature for 20 hours. After the reaction solution was concentrated under the reduced pressure, the residue was dissolved again in dichloromethane, and washed with aqueous ammonia. The aqueous layer was further extracted with dichlbromethane. The combined organic layer was dried over sodium sulfate, the solvent was distilled off under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate] to obtain 897 mg of 2-methyl-4-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-1,5-naphthyridine and 220 mg of 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine (compound No. 46) as reddish white amorphous powder. These have the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 2.54 (3H,s), 4.42 (2H,d,J=5.9Hz), 6.41 (1H,s), 6.85 (1H,broad t), 6.91-7.53 (23H), 7.97 (1H,dd,J=7.0Hz,1.6Hz), 8.17 (1H,dd,J=8.5Hz,1.7Hz), 8.55 (1H,dd,J=4.1Hz,1.7Hz)

2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine (compound No. 46)

^{1}H NMR δppm ($CDCl_3$) 2.60 (3H,s), 4.55 (2H,d,J=5.7Hz), 6.46 (1H,s), 6.96 (1H, broad t), 7.19 (2H,d,J=8.2Hz), 7.32 (2H,d,J=8.2Hz), 7.44-7.57 (4H), 7.91 (1H,dd,J=7.0Hz,2.2Hz), 8.18 (1H,dd,J=8.6Hz,1.7Hz), 8.64 (1H,dd,J=4.2Hz,1.7Hz)

EXAMPLE 10

Preparation of 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine (compound No. 48)

4-Chloro-2-ethyl-1,5-naphthyridine was prepared from 3-aminopyridine and ethyl propionylacetate according to the method described in J.Royal Netherlands Chem.Soc., 95, 220 (1976). This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.42 (3H,t,J=7.6Hz), 3.02 (2H,q,J=7.6Hz), 7.69 (1H,s), 7.69 (1H,dd,J=8.4Hz,4.4Hz), 8.37 (1H,dd,J=8.4Hz,1.7Hz), 9.02 (1H,dd,J=4.4Hz,1.7Hz)

A reaction solution of 325 mg of 4-chloro-2-ethyl-1,5-naphthyridine and 5 ml of phenol was heated to 180°C for 2 hours while ammonia gas was blowing therein. The temperature was lowered to about 100°C, the phenol was distilled off under the reduced pressure, the residue was dissolved in dichloromethane, and washed with 2 N NaOH. The aqueous layer was further extracted with dichloromethane, the combined organic layer was dried over sodium sulfate, and the solvent was distilled off under the reduced pressure to obtain 290 mg of 4-amino-2-ethyl-1,5-naphthyridine as pale brown solid. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.36 (3H,t,J=7.6Hz), 2.87 (2H,q,J=7.6Hz), 5.46 (2H,broad s), 6.68 (1H,s), 7.55 (1H,dd,J=8.4Hz,4.1Hz), 8.22 (1H,dd,J=8.4Hz,1.5HZ), 8.69 (1H,dd,J=4.1Hz,1.5Hz)

290 Mg of 4-amino-2-ethyl-1,5-naphthyridine, 0 58 ml of di-t-butyl dicarbonate and 102 mg of 4-dimethylaminopyridine were dissolved in 5 ml of pyridine, and this solution was heated to 50°C for 15 hours. The reaction solution was concentrated under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate-hexane (1:1)] to obtain 338 mg of 4-N-t-butoxycarbonylamino-2-ethyl-1,5-naphthyridine as pale brown oily material. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.41 (3H,t,J=7.6Hz), 1.59 (9H,s), 2.98 (2H,q,J=7.6Hz), 7.62 (1H,dd,J=8.4Hz,4.2Hz), 8.20 (1H,s), 8.29 (1H,dd,J=8.4Hz,1.6Hz), 8.75 (1H,dd,J=4.2Hz,1.6Hz), 9.04 (1H,broad s)

335 Mg of 4-N-t-butoxycarbonylamiono-2-ethyl-1,5-naphthyridine and 1 g of [2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide were dissolved in 5 ml of dimethylformamide, and 74 mg of 60 % oily sodium hydride was added while stirring at room temperature. After evolution of hydrogen gas ceased, the reaction temperature was heated to 50°C, and stirring was continued for 20 hours. The solvent was distilled off under the reduced presure, and the residue was purified by silica gel column chromatography [ethyl acetate-hexane (2:3)] to obtain 657 mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-ethyl-1,5-naphthyridine as pale yellow solid. This has the following NMR spectrum.

^{1}H NMR δppm ($CDCl_3$) 1.24 (3H,t,J=7.5Hz), 1.35 (9H,s), 2.86 (2H,q,J=7.5Hz),

4.97 (2H,s), 6.89-7.51 (22H), 7.08 (1H,s), 7.62 (1H,dd,J=8.3Hz,4.0Hz), 7.86 (1H,dd,J=7.6Hz,1.6Hz), 8.36 (1H,broad d,J=8.3Hz), 8.95 (1H,dd,J=4.0Hz,1.4Hz)

648 Mg of 4-N-t-butoxycarbonyl-N-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-2-ehthyl-1,5-naphthyridine was dissolved in 5 ml of dichloromethane, and 1 ml of trifluoroacetic acid was added to stir at room temperature for 20 hours. After the reaction solution was concentrated under the reduced pressure, the residue was dissolved again in dichloromathane, and washed with aqueous ammonia. The aqueous layer was further extracted with dichloromethane. The combined organic layer was dried over sodium sulfate, the solvent was distilled off under the reduced pressure, and the residue was purified by silica gel column chromatography [ethyl acetate) to obtain 348 mg of 2-ethyl-4-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-1,5-naphthyridine and 50 mg of 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine (compound No. 48) as pale yellow solid. These have the following NMR spectrum.

2-ethyl-4-[2'-(1-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methylamino-1,5-naphthyridine

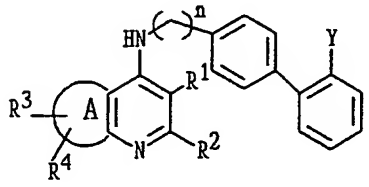
^{1}H NMR δppm ($CDCl_3$) 1.33 (3H,t,J=7.5Hz), 2.82 (2H,q,J=7.5Hz), 4.44 (2H,d,J=5.7Hz), 6.46 (1H,s), 6.94 (1H,broad t), 6.91-7.55 (23H), 7.96 (1H,dd,J=7.3Hz,1.9Hz), 8.20 (1H,dd,J=8.5Hz,1.8Hz), 8.56 (1H,dd,J=4.2Hz,1.8Hz)

2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine (Compound No. 48)

^{1}H NMR δppm ($CDCl_3$) 1.37 (3H,t,J=7.6Hz), 2.89 (2H,q,J=7.6Hz), 4.57 (2H,d,J=5.7Hz), 6.50 (1H,s), 7.03 (1H,broad t), 7.20 (2H,d,J=8.2Hz), 7.33 (2H,d,J=8.2Hz), 7.43-7.59 (4H), 7.91 (1H,dd,J=7.3Hz,1.9Hz), 8.29 (1H,broad d, J=8.3Hz), 8.65 (1H,dd,J=4.3Hz,1.6Hz)

CLAIMS

1. A 4-aminoquinoline represented by the general formula:



wherein A is benzene, pyridine, pyridazine, pyrimidine or pyrazine ring, wherein each ring is fused to the pyrizine ring;

R^1 and R^2 are independently a C_1-C_8 alkyl group, a C_2-C_8 alkenyl group, a C_2-C_8 alkynyl group or CF_3 group;

Y is a 1H-tetrazol-5-yl group or an alkali metal salt therof, a $-CO_2R^5$ group, a -CONR'R" group or a $-CONHSO_2R^6$ group;

R^3 and R^4 are independently hydrogen atom, an optionally substituted C_1-C_8 alkyl group, a C_1-C_8 alkoxy group, hydroxy, a halogen atom, -CN group, a $-SO_2NR'R"$ group, a $-CO_2R^5$ group, a -CONR'R" group or a $-CONHSO_2R^6$ group, or a 1H-tetrazol-5-yl group or an alkali metal salt thereof;

R^5 is hydrogen atom, an alkali metal atom or a C_1-C_8 alkyl group;

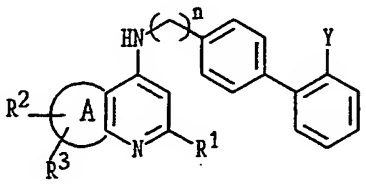
R^6 is a C_1-C_8 alkyl group, a C_3-C_{10} cycloalkyl group or an aryl group;

R' and R" are independently hydrogen atom or a C_1-C_8 alkyl group, or R' and R" together form an alicyclic struxture; and

n is o, 1 or 2,

or a pharmacologically acceptable ester or salt thereof.

2. A pharmaceutical composition for preventing or treating hypertension or congestive heart failure which comprises as an active ingredient an 4-aminouqinoline represented by the general formula:



wherein A is benzene, pyridine, pyridazine, pyrimidine or pyrazine ring, wherein each ring is fused to the pyridine ring;

R^1 and R^2 are independently a C_1-C_8 alkyl group, a C_2-C_8 alkenyl group, a C_2-C_8 alkynyl group or -CF_3 group;

Y is a 1H-tetrazol-5-yl group or an alkali metal salt thereof, a -CO_2R^5 group, a -CONR'R" group or a -$CONHSO_2R^6$ group;

R^3 and R^4 are independently hydrogen atom, an optionally substituted C_1-C_8 alkyl group, a C_1-C_8 alkoxy group, hydroxy, a halogen atom, -CN group, a -$SO_2NR'R"$ group, -CO_2R^5 group,

-CONR'R" group, a -$CONHSO_2R^6$ group or a 1H-tetrazol-5-yl- group or alkali metal salt thereof;

R^5 is hydrogen atom, an alkali metal atom or a C_1-C_8 alkyl group;

R^6 is a C_1-C_8 alkyl group, a C_3-C_{10} cycloalkyl group or an aryl group;

R' and R" are independently a hydrogen atom or a C_1-C_8 alkyl group, or R' and R" together form an alicyclic structure; and

n is 0, 1 or 2,

or a pharmacologically acceptable ester or salt thereof.

3. A compound of Claim 1, selected from the group consisting of:

1) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline,

2) 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]amino-2-methylquinoline,

3) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

4) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethylquinoline,

5) 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

6) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-n-propylquinoline,

7) 2-n-propyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

8) 2-n-butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]aminoquinoline,

9) 2-n-butyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

10) 2-n-pentyl-4-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

11) 2-trifluoromethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

12) 2-(1-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

13) 2-(2-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

14) 2-(2-propynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

15) 2-(2-butenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

16) 2-(2-butynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

17) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2,8-dimethylquinoline,

18) 2,8-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

19) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-8-methoxy-2-methylquinoline,

20) 8-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)methyl]aminoquinoline,

21) 8-ethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

22) 2-methyl-8-n-propyl-4-[(2'-(tetrazol-5-yl)methyl]aminoquinoline,

23) 2-methyl-8-isopropyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

24) 4-[2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-5-dimethylaminosulfonylquinoline,

25) 2-methyl-5-dimethylaminosulfonyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

26) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-5-morpholinosulfonylquinoline,

27) 2-methyl-5-morpholinosulfonyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

28) 2-methyl-5-piperidinosulfonyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

29) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-6-cyano-2-methylquinoline,

30) 6-cyano-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

31) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline-6-carboxylic acid,

32) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylic acid,

33) 6-carbamoyl-4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methylquinoline,

34) 6-carbamoyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

35) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-6-(tetrazol-5-yl)-quinoline,

36) 2-methyl-6-(tetrazol-5-yl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

37) 6-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

38) 4-[(2'-(N-methanesulfonyl)carbamoylbiphenyl-4-yl)methyl]amino-2-methylquinoline,

39) 2,7,8-trimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

40) 8-trifluoromethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline.

41) ethyl 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethylquinoline-6-carboxylate,

42) ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline-6-carboxylate,

43) 2,3-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

44) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

45) 4-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

46) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

47) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethyl-1,5-naphthyridine,

48) 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

49) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-n-propyl-1,5-naphthyridine,

50) 2-n-propyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

51) 2-n-butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]amino-1,5-naphthyridine,

52) 2-n-butyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

53) 2-n-pentyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

54) 2-trifluoromethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

55) 2-(1-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

56) 2-(2-propenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

57) 2-(2-propynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

58) 2-(2-butenyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

59) 2-(2-butynyl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

60) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2,8-dimethyl-1,5-naphthyridine,

61) 2,8-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

62) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-8-methyoxy-2-methyl-1,5-naphthyridine,

63) 8-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)methyl]amino-1,5-naphthyridine,

64) 8-ethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

65) 2-methyl-8-n-propyl-4-[(2'-(tetrazol-5-yl)methyl]amino-1,5-naphthyridine,

66) 2-methyl-8-isopropyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

67) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-6-cyano-2-methyl-1,5-naphthyridne,

68) 6-cyano-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

69) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine-6-carboxylic acid,

70) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine-6-carboxylic acid,

71) 6-carbamoyl-4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

72) 6-carbamoyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

73) 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-methyl-6-(tetrazol-5-yl)-1,5-naphthyridine,

74) 2-methyl-6-(tetrazol-5-yl)-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

75) 6-methoxy-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

76) 4-[(2'-(N-methanesulfonyl)carbamoylbiphenyl-4-yl)methyl]amino-2-methyl-1,5-naphthyridine,

77) 2,7,8-trimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

78) 8-trifluoromethyl-2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-ytl)methyl]amino-1,5-naphthyridine,

79) ethyl 4-[(2'-carboxybiphenyl-4-yl)methyl]amino-2-ethyl-1,5-naphthyridine-6-carboxylate,

80) ethyl 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine-6-carboxylate,

81) 2,3-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

82) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,7-naphthyridine,

83) 6-methyl-8-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-pyrido[2,3-d]pyrimidine,

84) 6-methyl-8-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-pyrido[2,3-b]pyrazine,

85) 2-methyl-4-[2'-(tetrazol-5-yl)biphenyl-4-yl]aminoquinoline,

86) 2-ethyl-4-[2'-(tetrazol-5-yl)biphenyl-4-yl]aminoquinoline.

4. A compound of Claim 1, wherein:

A is phenyl or pyridyl,

R_1 is H, CH_3 or CO_2CH_3,

R_2 is CH_3 or C_2H_5,

R_3 is H,

R_4 is H, and

n is 0 or 1.

5. A compound of Claim 4 selected from the group consisting of:

3) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

5) 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

43) 2,3-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]aminoquinoline,

46) 2-methyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

48) 2-ethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

81) 2,3-dimethyl-4-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]amino-1,5-naphthyridine,

85) 2-methyl-4-[2'-(tetrazol-5-yl)biphenyl-4-yl]aminoquinoline, and

86) 2-ethyl-4-[2'-(tetrazol-5-yl)biphenyl-4-yl]aminoquinoline.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/04201

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D215/42; C07D401/12; C07D471/04; A61K31/47

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,9 107 404 (IMPERIAL CHEMICAL INDUSTRIES PLC) 30 May 1991 see claims	1
X	EP,A,0 412 848 (IMPERIAL CHEMICAL INDUSTRIES PLC) 13 February 1991 cited in the application see claims	1
A	US,A,3 272 824 (THE NORWICH PHARMACAL COMPANY) 13 September 1966 * page 1 *	1
P,X	WO,A,9 119 697 (MEJI SEIKA KABUSHIKI KAISHA) 26 December 1991 * page 41: compound 33 *	1

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 AUGUST 1992	12.09.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9204201 SA 61018

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9107404	30-05-91	AU-A- 6733690	13-06-91
		EP-A- 0454831	06-11-91
		US-A- 5126344	30-06-92
EP-A-0412848	13-02-91	AU-B- 623546	14-05-92
		AU-A- 6095590	14-02-91
		CN-A- 1050187	27-03-91
		GB-A- 2234748	13-02-91
		JP-A- 3169863	23-07-91
US-A-3272824		BE-A- 640817	01-04-64
		GB-A- 1010254	
WO-A-9119697	26-12-91	AU-A- 8066691	07-01-92
		EP-A- 0487745	03-06-92